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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 08/808,827
Filing Date: February 28, 1997
Appellant(s): GUNZBURG ET AL.

Arles A. Taylor, Jr.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 26 August 2005 and the supplemental appeal brief filed 20 December 2005 appealing from the Office action mailed 26 October 2004.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner.

Minor corrections in the rejections detailed below have been made relative to the Office action mailed 26October 2004. Claims 12, 39, and 62 are no longer rejected under combinations of references that do not include Price et al. in view of the limitation in the claims that the coding region of a beta galactosidase gene in the body of the vector is operably linked to the

recombinant U3 region. Previously maintained rejections of claims 12, 39, and 62 over combinations of references including Price et al. are maintained. The last three rejections listed below under combinations of references that include either Miller et al. and Panganiban et al., or Price et al., or Longmore et al. and Kay et al. have been modified to indicate that the rejected claims are cited under one of the listed combinations rather than any of the listed combinations.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Couture et al. Retroviral Vectors Containing Chimeric Promoter/Enhancer Elements Exhibit Cell-Type-Specific Gene Expression. Human Gene Therapy Vol. 5, pages 667-677 (1994)

Faustinella et al. A New Family of Murine Retroviral Vectors with Extended Multiple Cloning Sites for Gene Insertion. Human Gene Therapy Vol. 5, pages 307-312 (1994)

Mee et al. Construction and hormone regulation of a novel retroviral vector. Gene Vol. 88, pages 289-292 (1990)

Mehigh et al. Development of a Recombinant Bovine Leukemia Virus Vector for Delivery of a Synthetic Bovine Growth Hormone-Releasing Factor Gene into Bovine Cells. J. Anim. Sci. Vol. 71, pages 687-693 (1993)

Miller et al. Improved Retroviral Vectors for Gene Transfer and Expression. Biotechniques Vol. 7, pages 980-990 (1989)

Panganiban et al. (1984) The retrovirus pol gene encodes a product required for DNA integration: Identification of a retrovirus int locus. Proc. Natl. Acad. Sci. USA Vol. 81, pages 7885-7889

Price et al. Lineage analysis in the vertebrate nervous system by retrovirus-mediated gene transfer. Proc. Natl. Acad. Sci, USA Vol. 84, pages 156-160 (1987)

Longmore et al. Both Megakaryocytopoiesis and Erythropoiesis Are Induced in Mice Infected With a Retrovirus Expressing an Oncogenic Erythropoietin Receptor. Blood Vol. 82, pages 2386-2395 (1993)

Kay et al. In Vivo Gene Therapy of Hemophilia B: Sustained Partial Correction in Factor IX-Deficient Dogs. Science Vol. 262, pages 117-119 (1993)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC 103

Claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al.

The claims are drawn to a retroviral vector in which the 3' U3 region is partially replaced with a polylinker sequence that comprises a heterologous promoter and which further comprises a coding sequence in the body of the vector. In some embodiments the promoter insert also comprises an additional regulatory element or is regulated by transacting molecules, the LTR is derived from leukemia virus or sarcoma virus, the coding sequence is a marker gene, the recombinant promoter activity is cell specific. In some embodiments the claims are drawn to cells that produce the retroviral vectors, combinations of the retroviral vector and a packaging

cell line, the retroviral vector in a viral particle, and methods of infecting cells with the retroviral vector.

Couture et al. (Reference AS in the Form PTO-1449 filed 9/23/97) shows retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses, including leukemia and sarcoma retroviruses. Couture et al. shows in the abstract that the inserted region comprises an enhancer regulatory element and a promoter. Couture et al. shows on page 669 column 2 that the first 40 nucleotides of the original vector are retained in the substitution of the U3 region. The vector of Couture comprises a chloramphenicol acetyl transferase marker gene operably linked to the recombinant reporter and a neomycin resistance gene. Couture et al. shows in the abstract that after packaging, the substituted U3 region appears at the 5' LTR and serves as a promoter for all genes in the body of the vector, and that different LTR constructs were preferentially expressed in specific cell types. Couture et al. states in the second paragraph of the Results section on page 669 that U3 regions are bound by cellular factors. Couture et al. shows in Table 3 that their chimeric LTR promoters are active in a cell type specific manner. Couture et al. state on page 670 that promoter suppression or interference may occur within retroviral vectors containing internal promoter elements. Couture et al. states on page 667 that retroviral vectors with target cell specificity have utility in gene therapy protocols. Couture et al. shows the use of packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors into retroviral particles. Couture et al. does not show a vector comprising a multiple cloning site in the U3 region.

Faustinella et al. shows in figure 1 Moloney murine leukemia retroviral vector pS3. pS3 comprises a partial deletion of the 3' U3 region, into which has been inserted a polylinker with

unique cloning sites, for example the Bsa AI site and the Nae I site used to construct the vectors of figure 2.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vectors of Couture et al. by adding the multiple cloning site of Faustinella et al. because Faustinella et al. shows that multiple cloning sites may be used to insert sequences of choice in a U3 region of a retroviral vector.

Claims 1, 5, 7, 9, 11, 16-25, 28, 29, 31, 32, 56-59, 61, 65-72, and 74-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above, and further in view of Mee et al.

The claims are drawn to retroviral vectors comprising mouse mammary tumor virus promoters or regulatory elements.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above does not show mouse mammary tumor virus (MMTV) promoters or regulatory elements.

Mee et al. shows a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone. Mee et al. state on page 292 that their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. in view of Faustinella et al. as applied

to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above by insertion of an MMTV promoter region in a deleted 3' U3 region of a retroviral vector because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types.

Claims 1, 5, 7, 9, 11, 15-25, 28, 29, 31-36, 38, 42-49, and 51-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above, and further in view of Mehigh et al.

The claims are drawn to retroviral vectors comprising cellular promoters or regulatory elements.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above does not show cellular promoters or regulatory elements.

Mehigh et al. shows a retroviral vector comprising a whey acidic acid protein (WAP) promoter. Mee et al. states in the abstract that their vector allows for inducible expression from the WAP promoter of an operably linked gene in MBDK cells and may prove useful as a delivery system for peptides in cattle to increase milk production.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above by insertion of a WAP promoter region in a deleted 3' U3 region of a retroviral vector because Mehigh et al.

shows that such vectors are inducibly expressed and may allow for increased milk production in cattle.

Claims 1, 13, 14, 33, 40, 41, 56, 63, and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over one of:

1)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above,

2)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above, and further in view of Mee et al. as applied to claims 1, 5, 7, 9, 11, 16-25, 28, 29, 31, 32, 56-59, 61, 65-72, and 74-78,

3) Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above, and further in view of Mehigh et al. as applied to claims 1, 5, 7, 9, 11, 15-25, 28, 29, 31-35, 38, 39, 42-49, and 51-55;

where each of the above three are as evidenced by Miller et al. and Panganiban et al.

The claims are drawn to retroviral vectors comprising an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

The three combinations of references cited above do not explicitly show an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

Couture et al. shows in figure 1 a retroviral vector LCSN and a derivative of LCSN. Couture et al. shows in the Methods section on page 668 that their vectors are derivatives of the vectors of Miller et al.

Miller et al. shows in figure 2 that their vectors retain the phi+ packaging sequence, but lack the gag, pol, and env genes of a replication-competent retrovirus.

Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus.

Therefore the vectors of claims 13 and 14 are taught by the above cited combinations of references as evidenced by Miller et al. and Panganiban et al.

Claims 1, 10, 12, 33, 37, 39, 56, 60 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over one of:

1)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above,

2)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above, and further in view of Mee et al. as applied to claims 1, 5, 7, 9, 11, 16-25, 28, 29, 31, 32, 56-59, 61, 65-72, and 74-78,

3) Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above, and further in view of Mehigh et al. as applied to claims 1, 5, 7, 9, 11, 15-25, 28, 29, 31-35, 38, 39, 42-49, and 51-55;

where each of the above three are further in view of Price et al.

The claims are drawn to BAG retroviral vectors or retroviral vectors comprising a beta galactosidase reporter gene.

The three combinations of references cited above do not explicitly show retroviral vectors derived from BAG vectors or coding sequences linked to the recombinant promoter that is a beta galactosidase gene.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of the above cited combinations of references by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

Claims 17, 20, 21, 26, 28, 43, 50, 51, 52, 53, 66, 73, 74, 75, and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over one of:

1)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above,

2)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above, and further in view of Mee et al. as applied to claims 1, 5, 7, 9, 11, 16-25, 28, 29, 31, 32, 56-59, 61, 65-72, and 74-78,

3) Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 above, and further in view of Mehigh et al. as applied to claims 1, 5, 7, 9, 11, 15-25, 28, 29, 31-35, 38, 39, 42-49, 51-55, 79-82, 84, 85, 88-95, and 97-101;

where each of the above three are further in view of Longmore et al. and Kay et al.

The claims are drawn to the use of retroviral vectors in animals.

The three combinations of references cited above do not show use of retroviruses in animals.

Longmore et al show in the abstract that mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes.

Kay et al. shows in the abstract and throughout that hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of the combinations of references cited above to express a therapeutic protein because both Kay et al. and Longmore et al. show that retroviral vectors may be used to express therapeutically effective levels of a recombinant protein in an animal.

(10) Response to Argument

On pages 16-20 of the Appeal Brief filed 20 December 2005 the appellants state that Couture et al. does not show a partially deleted U3 region. However Couture et al. shows a chimeric U3 region that was created by first deleting a portion of the original U3 region of the MuMLV based vector and substituting portions of U3 regions from six different murine leukemia viruses. It is noted that the region deleted by Couture includes the original promoter region of the U3 region as noted in the abstract of Couture et al. Figure 3 of Couture et al. details the differences in sequence of the resulting U3 regions at the sequence level from the starting U3

region. The appellants equate the claimed partially deleted U3 region with an incomplete U3 region, however this is not correct and claims 1, 17, 28, 56, 66 do not require an incomplete or defective U3 region. Couture et al. first deleted a region of the original U3 region as required by claims 1, 17, 28, 56, 66 and then inserted a substitute sequence that restored function to the 3' LTR consisting of an LTR sequence from a different murine leukemia retrovirus. It is apparent that the appellants wish to claim a combined deletion/substitution LTR in the mouse mammary tumor virus embodiment of claim 7 (as disclosed in the example of pages 21-22 of the instant specification). The appellants contest this on pages 19-20 of their arguments, however they do not show why claim 1 or the explicitly claimed substituted U3 region in claim 7 do not read on substitutions of a U3 region.

The appellants state on pages 20-25 that Couture et al. does not provide motivation to use the polylinker of Faustinella et al. However Faustinella et al. provides motivation to use a polylinker in a 3' U3 region in other vectors because Faustinella et al. shows that such a polylinker can be used to provide convenient restriction endonuclease sites to allow for insertion of sequences that are expressed upon infection. Couture et al. shows use of restriction endonuclease sites to aid in construction of their deletion/insertion U3 region, and so the use of the polylinker is compatible with the purpose of Couture et al. in construction of recombinant U3 regions. The appellants further argue that Faustinella et al. teaches away from insertion of promoters into a U3 polylinker because Faustinella et al. inserts a promoter operably linked to a coding sequence. However the particular insert used by Faustinella et al. does not directly teach away from use of other inserts, such as the LTR promoter inserted into the U3 region by Couture et al.

The appellants discussion of claim 12 on page 26, 39 on page 53, and 62 on page 30 does not consider the rejection of claim 12 over combinations of references that include Price et al.. Price et al. shows retroviral vectors with a beta galactosidase reporter gene operably linked to an LTR promoter and makes obvious the limitations of claim 12.

The discussion of claims 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 on pages 25- 33 is reiterative of the arguments concerning Couture et al. in view of Faustinella et al. and have been addressed above.

The discussions of the rejections involving the Mee et al., Mehigh et al., Miller et al., Panganaban et al., Price et al., Longmore et al., and Kay et al. references on pages 34-88 are reiterative of the arguments concerning the Couture et al. and Faustinella et al. combination and have been addressed above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

25 February 2016

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